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09/673,871	10/20/2000	Alexandre Marti	NITROS P146US	6986

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EXAMINER

CHONG, YONG SOO

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Art Unit: 1617

DETAILED ACTION

Status of the Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/27/2005 has been entered.

This Office Action is in response to applicant's remarks filed on 12/23/2005. Claims 19-27, 29-53 are pending. Claims 19-27, 29-35 have been amended. Claims 36-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant's election **without traverse** of the restriction requirement in the reply filed on 12/23/2006 is acknowledged. The requirement is deemed proper and is therefore made FINAL. Claims 19-27, 29-35 are examined herein insofar as they read on the elected invention and species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim(s) 20, 24-25, 31-35 is/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

Art Unit: 1617

subject matter which applicant regards as the invention. Specifically, claim(s) 20, 24-25, 31-32 recites the limitation "solution." There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 19-27, 29-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gierskcky et al US Patent 6,034,267.

Gierskcky et al teaches pharmaceutical compositions for treating or diagnosing a condition comprising an ester of Aminolevulanic acid (AIA). (see abstract, claim 1) and a pharmaceutical carrier or excipient (claim 8). The concentration of the compounds in Gierskcky's compositions depends upon the nature of the compound, the composition, mode of administration, and the patient and may be varied or adjusted according to

Art Unit: 1617

choice. Generally, however, concentration ranges of 1 to 50% are suitable (see col 6, lines 25-33). Gierskcky also teaches the use of chelating agent such as EDTA, deferoxamine, or alike in his compositions (see col 7, lines 21-33). Gierskcky teaches methods of preparing and using ALA hexyl ester (see example 4, and 15).

Gierskcky fails to specifically use concentrations of ALA-esters in amounts less than 1% and further specify the instant ranges of pH.

However, it is well established that merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Becket*, 33 USPQ. 33 (C.C.P.A. 1937). *In re Russell*, 439 F.2nd 1228, 169 U.S.P.Q. 426 (C.C.P.A. 1971). Accordingly, absence of showing a criticality, it would have been *prima facie* obvious to optimize the concentration of Gierskcky's ALA-esters and their respective pH ranges, because it has been held that the ordinary artisan would have had a reasonable expectation of success in achieving the desirable clinical outcome by modifying the such values.

Response to Arguments

Applicant's arguments with respect to this rejection have been fully considered but are not found persuasive.

Applicant first argues that there is no suggestion to one of ordinary skill in the art to prepare an ester of 5-aminolevulinic acid at a concentration of less than 1% by weight.

In response, Examiner states that contrary to Applicant's reasoning modification of proportions and ranges is not patentable, as a matter of law, unless there is a

Art Unit: 1617

showing of criticality. See *In re Becket*, 33 USPQ, 33 (CCPA 1937). *In re Russell*, 439 F.2d 1228, 169 U.S.P.Q. 426 (CCPA 1971). Applicant has not met the burden of showing that the instantly claimed ranges are critical to operation of preparing a solution that contains an ester of 5-ALA. Furthermore, mere optimization of ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also *In re Peterson*, 315 F. 3d at 1330, 65 USPQ 2d at 1382 "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." MPEP 2114.04.

Nonetheless, Gierskcky et al. has provided a suggestion and motivation for modifying or adjusting the concentration ranges of the employed compounds. The concentration of the compounds in Gierskcky's compositions depends upon the nature of the compound, the composition, mode of administration, and the patient and may be varied or adjusted according to choice. Generally, however, concentration ranges of 1 to 50% are suitable (see col 6, lines 25-33). Therefore, the range of 1 to 50% is merely a preferred range and is by no means bound to that particular range.

Applicant argues that at the priority date of the subject application, the concentrations of ALA-esters studied were about two orders of magnitude higher than

Art Unit: 1617

presently claimed. Specifically, Applicants cite Peng et al., who administered ALA esters in a concentration of about 20% (w/w).

In response, Gierskcky et al. teaches pharmaceutical compositions for treating or diagnosing a condition comprising an ester of ALA. (see col 3, lines 1-30). Gierskcky teaches the concentrations of the compounds in Gierskcky's compositions are generally about 1 to 50% (see except the instantly claimed ranges of ALA esters. (col 6, lines 24-33). Gierskcky also teaches the use of chelating agent such as deferroxamine or alike in his compositions (see col 7, lines 21-33). Gierskcky teaches methods of preparing and using ALA hexyl ester (see example 4, and 15). All elements of the instant claims are described in Gierskcky, except the instantly claimed ranges ester of ALA. But as the matter of law, absence of showing a criticality, it would have been *prima facie* obvious to optimize the concentration of Gierskcky's ALA-esters and their respective pH ranges to achieve a desirable clinical outcome. Therefore, the difference is not about two orders of magnitude higher than presently claimed. Gierskcky et al. would have had a reasonable expectation of success for preparing a composition comprising ALA esters of less than 1% by weight for use in either photochemotherapy or diagnosis.

Applicant also adds that no knowledge generally available to one of ordinary skill in the art to arrive at the claimed concentrations of ALA-ester doses lower than 1%. (see Arguments at page 7, 5th para.). However, Examiner states that contrary to such statement applicant's declaration contains articles by Lang et al, Qian Peng et al and Marti et al that esterified aminolevulinic acid derivatives induces porphyrin fluorescence in skin. Such teachings were available to one of ordinary skill in the art because the

Art Unit: 1617

artisans before filing of the instant Application knew them. Accordingly, optimizing the concentrations of a formulation to achieve such end-result would have been within the skill of the ordinary level in the art and available at the time of claimed invention. (see Applicant's Declaration filed on January 16, 2004, paragraph 12-14).

Further, the Declaration under 37 CFR 1.132 filed January 16, 2004 is insufficient to overcome the rejection of claim 19-27, 29-35 based upon Gierskcky as set forth in the last Office action because: it is not commensurate with the scope of the claims and does not provide adequate data comparing the formulations of Grierskcky to establish unexpected or criticality of lower ranges ALA esters of the claimed invention.

As the initial matter the opinion declaration explains methods of using esters of ALA at a lower concentrations as conventionally employed in the art at the time of publication of the cited references. Such studies did not describe unexpected observations in formulating lower concentrations of esterified ALA. Therefore, Applicant's arguments that preparing a formulation of esterified 5-ALA is not commensurate with the scope of the claims, because the instant claims are not directed to methods of using such compositions.

Finally, Applicant argues that it was unexpected that lower doses of ALA esters would produce higher levels of PpIX than the known lowest doses of ALA esters studied at the time of the present invention. Specifically, attention is drawn to Exhibit E, where a graph of ALA esters (concentration) vs PpIX fluorescence is shown.

After closer examination of the graph, Examiner argues that these results are not unexpected because the maximum fluorescence of ALA-ethylester and ALA are above

Art Unit: 1617

1% in concentration. The ALA-octylester is inconclusive because there were precipitation problems at concentrations higher than 0.1%. The ALA-butylester still shows significant fluorescence well above 1%. In fact, ALA-hexylester is the only one that shows the entire fluorescence range well below 1%. With results like this, it is obvious to optimize the concentration below 1%, especially because of the fluorescence results for several ALA esters at or around 1% concentration.

Examiner also adds that the argument involving the Marti et al. reference will not be considered because it was not known at the time of invention. The reference was published after the filing date of the instant invention.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

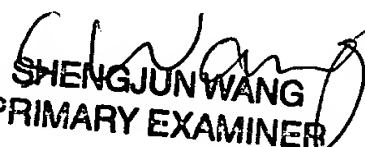
Art Unit: 1617

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC


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PRIMARY EXAMINER